

## REMARKS

Applicants submit this Amendment in response to the Office Action mailed February 26, 2001. With entry of this Amendment, claims 1-29 are pending in the application. Claims 11-22, and 26 and 27 are withdrawn following the response to the Restriction Requirement. Applicants hereby affirm the election of Group I, claims 1-10, 23-25, 28 and 29. The claims have been amended as discussed below, and no new matter is added. These claim amendments are fully supported by the specification. Specifically, support for claim 2 may be found, e.g., at page 17, line 25. Entry of these amendments is respectfully requested.

1. Claim 1 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. The Examiner has pointed out that there is insufficient antecedent basis for “said amino acids about 197 and about 236 are joined by a peptide bond” in lines 8-9 of claim 1(c). Applicants have amended claim 1 accordingly and submit that this ground of rejection can be withdrawn.

2. The Examiner states that it is unclear what SEQ ID NO: the amino acids “about 197-236” of 1(c), and both “197 and about 236” as well as “288 and about 336” of 1(e) are referring to. Claim 1(c) states “a polynucleotide encoding amino acids from about 1 to about 197 and about 236 to about 373 of SEQ ID NO:2, wherein said amino acids”, the “wherein said” clearly providing reference to the amino acids of SEQ ID NO:2. Claim 1(e) states “a polynucleotide encoding amino acids from about 1 to about 197 and about 236 to about 288, and amino acids about 336 to about 373 of SEQ ID NO:2, wherein said amino acids”, the “wherein said” also clearly providing reference to the amino acids of SEQ ID NO:2. However, if the Examiner still feels that this is not clear, additional reference to SEQ ID NO:2 can be added. Given the above remarks, Applicants respectfully request withdrawal of the rejection.

3. The Examiner has kindly pointed out that it is unclear what SEQ ID NO: the amino acids “about 288 and about 336” are referring to. Applicants have amended claim 1(d) accordingly to include “said”, thus referencing the amino acids of SEQ ID NO:2. Applicants submit that this ground of rejection can be withdrawn.

4. Claims 23-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. The Examiner points out that in claim 23, the length of the complement nucleotide sequence cannot

be both 1122 nucleotides and between 8 and 50 nucleotides. Applicants have amended claim 23 and submit that this ground of rejection can be withdrawn.

5. Claims 1 and 5-10 are rejected under 35 U.S.C. § 112, second paragraph, as containing subject matter which allegedly is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

The Examiner alleges that the specification does not describe or disclose the elements which are essential to various functions of the claimed invention, including:

- defining the length of the nucleic acid and amino acid molecules. The Applicants respectfully argue that the subject matter is described in the specification and refer the Examiner to, for example, page 17, lines 21-28, and lines 4-20, for the definitions of preferred lengths of nucleic acid and amino acid molecules of the invention, respectively.

- defining the number of modifications within these molecules. The Applicants respectfully argue that the subject matter is described in the specification and refer the Examiner to, for example, page 11, lines 16-28, page 12, lines 9-19, and page 13, lines 1-10.

- defining the nature, number, and permissible changes of conservative amino acid substitutions of SEQ ID NO:2. The Applicants respectfully argue that the subject matter is described in the specification and refer the Examiner to, for example, page 16, lines 27-28, and page 15, lines 16-25, for the definitions of the nature and number and permissible changes of conservative amino acid substitutions of the invention, respectively.

- what comprises at least 80% identity. The Applicants respectfully argue that the subject matter is described in the specification and refer the Examiner to, for example, page 11, lines 24-28.

- what distinguishing attributes are concisely shared by the member of the genus, what attributes are concisely shared by conservative amino acid substitutions of SEQ ID NO:2, and what could distinguish structures within the genus from others. The Applicants respectfully argue that the specification teaches and adequately describes the subject matter and refer the Examiner to, for example, page 15, lines 16-28 and page 16, lines 1-3.

6. Claims 23-25, 28 and 29 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of inhibiting cell growth *in vitro*, allegedly does not reasonably provide enablement for methods of inhibiting cell growth *in vivo* because of the state of and the unpredictability of the art. Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

With regard to gene therapy, Applicants respectfully disagree with the Examiner's characterization of the unpredictability of gene therapy, and with the implied assertion that Applicants must provide human gene therapy data. As noted above, the Examiner alleges that undue experimentation would be required before one skilled in the art may utilize the disclosed antisense and ribozymes targeting Nogo B to inhibit cell growth *in vivo* in a gene therapy method, and that the specification does not present specific guidance or working examples of the use of antisense and ribozymes targeting Nogo B in a therapeutic method.

Applicants respectfully traverse this rejection and its bases. For enablement purposes, a specification need not teach what is well known in the art. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Moreover, some amount of experimentation is not fatal as long as the amount is not undue. *Id.* For the instant claims, no undue experimentation is required, because the specification provides sufficient guidance to allow one having ordinary skill in the art to make and use vectors or a gene transfer vehicle comprising antisense and ribozymes targeting Nogo B, for gene delivery according to the claimed methods. More specifically, the specification details how to construct such a vector or vehicle (*see* for example, page 18, line 2 through page 19, line 4 and page 28, line 5 through page 30, line 11). Further, contrary to the assertions of the Examiner regarding lack of examples demonstrating therapeutic methods, Applicants submit that there is no requirement that Applicants provide data for every therapeutic method (*see Amgen v. Chugai and Genetics Institute*, 927 F.2d 1200 (Fed. Cir. 1991)). It is well established that examples are not required for an enabling disclosure. *In re Robins*, 166 U.S.P.Q. 552 (C.C.P.A. 1970); *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970). The first paragraph of § 112 requires nothing more than objective enablement, which Applicants have provided.

It is also respectfully submitted that a person having ordinary skill in the art of molecular biology can take any known antisense oligonucleotide or ribozyme and place it in an expression vector with only routine, not undue, experimentation. Further, the specification

details a variety of vectors which may be desirable to deliver to cells, for example, on page 28, line 5 through page 30, line 11. Therefore, contrary to the Examiner's assertion, the methods of the present invention are enabling for methods of delivering a variety of antisense oligonucleotide and ribozyme encoding vectors.

The thrust of the Examiner's rejection appears to be that the specification does not enable the use of the claimed methodologies due to a lack of evidence regarding their human implementation. If this is true, the Examiner is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (holding that where the Examiner rejected pharmaceutical compositions based on § 112, a § 101 rejection for lack of utility would also have been proper. *See also* "Legal Analysis Supporting Utility Examination Guidelines," 60 F.R. 36263, July 14, 1995).

Applicants respectfully submit that this rejection is improper in view of the USPTO Guidelines which indicate that if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof, almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. In no case has a Federal court required an Applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans.** (Emphasis added)

Here, the situation is analogous. The instant specification describes a method of effective gene delivery; whether the method will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability.

In further support of the contention that the claims are not enabled, the Examiner cites the Crystal, Schofield, Verma, Friedman, Palu et al., Branch, and Crooke references,

allegedly disclosing problems with gene therapy. While these references represent sweeping generalizations of gene therapy, these references emphasize only one side of the story. In this regard, to date there are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. It is wholly unfair to focus solely upon the technical hurdles faced by some in the field while ignoring the successes.

For example, Applicants wish to draw the Examiner's attention to the results of gene therapy to treat severe combined immunodeficiency, as disclosed by Blaese et al. (*Science* 270:475-480 (1995)). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. To this day both patients continue to display significant improvement in their immune system function. The results of this gene therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer context, Roth et al. (*Nature Medicine* 2(9):985-991 (1996)) have shown that a recombinant retroviral vector targets tumor cells *in vivo*. Moreover, this vector, which encodes the tumor suppressor p53, provided a sufficient level of p53 expression such that apoptosis, or programmed cell death, was triggered in these cells. Accordingly, retrovirus gene therapy was accomplished *in vivo*. More recently, Khuri et al. (*Nature Medicine* 6(8):879-885 (2000)) reported a successful gene therapy regimen in human cancer patients using ONYX-015, an oncolytic, chimeric group C adenovirus having a large deletion in the E1B gene.

With respect to X-linked severe combined immunodeficiency (*i.e.*, SCID-X1), Cavazzana-Calvo et al. (*Science* 288:669-672 (2000)), have demonstrated full correction of disease phenotype in patients treated by gene therapy protocols. Further, Kay et al. (*Nature Genetics* 24:257-261 (2000)) have demonstrated therapeutic efficacy in the treatment of Haemophilia B with AAV vectors carrying the gene that encodes factor IX.

Moreover, the successes of gene therapy are in no way limited to only these examples. This is pointed out, in fact, in one of the review articles cited by the Examiner,

Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible ... [and] most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. Taken together, the evidence is

overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies. Crystal, *Science* 270:404, 405 (1995).

Applicants respectfully submit that in view of the foregoing, a therapeutic method of gene delivery is adequately enabled by the instant application. Accordingly, as gene therapy as a whole clearly evidences enablement, and as Applicants have described similar, known methodologies such as antisense oligonucleotides and ribozymes, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 112, first paragraph, has been obviated and request that the Examiner withdraw this ground of rejection.

7. Claims 1-10, 28 and 29 are rejected under 35 U.S.C. § 102(e) as being anticipated by Bandman et al., U.S. Patent No. 5,858,708, issued January 12, 1999. (In a telephone conference with the undersigned, the Examiner indicated that the rejection relates to claim 29, not claim 27.) Bandman allegedly teaches a nucleic acid composition comprising polynucleotides encoding amino acids from SEQ ID NO:2, including from 10-50 contiguous nucleotides of SEQ ID NO:1, which encode Nogo B, and methods for inhibiting the expression of SEQ ID NO:2 (and hence the activity of Nogo B) and which methods comprise administration of antisense or ribozymes targeting SEQ ID NO:1. Applicants submit that Nogo B is only similar to the sequence taught in Bandman et al. at the C-terminal end, from about amino acids 186 to the end of the molecule. Furthermore, the identities shared between the sequences are not included within the scope of the amended claims. Nogo B and the sequences taught in Bandman appear to be distinct forms of a larger family of proteins. However, the methods and compositions in Bandman do not comprise the administration of the specific antisense oligonucleotides or ribozymes suitable for targeting Nogo B as taught in the present application, and therefore do not anticipate the claims as amended. Reconsideration and withdrawal of this rejection are respectfully requested.

8. Claims 1-10, 23-25, 28 and 29 (not 27 and 28) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bandman et al. and further in view of Milner et al. and James. The Examiner appears to base the combination of references, in part, on the alleged similarity between the nucleotide sequences of Bandman and the present invention. As stated in the previous paragraph addressing the rejection under § 102(e), Bandman et al. do not teach the nucleotide sequence of Nogo B, but merely other, distinct sequences of proteins in the same

family with some degree of identity, and, as pointed out by the Examiner, do not teach the use of antisense oligonucleotides comprising SEQ ID NOs:3-6. In *Winner International Royalty Corp. v. Wang*, No. 96-2107, 48 USPQ.2d 1139 (D.C.D.C 1998), the court held:

...invention cannot be found obvious unless there was some **explicit** teaching or suggestion in art to motivate one of ordinary skill to combine elements so as to create same invention. (emphasis added)

Milner et al. and James teach general methods of assessing the ability of antisense to inhibit expression of a target gene, however they do not explicitly teach or suggest the nucleotide or amino acid sequence of Nogo B nor suggest or teach the specific antisense nucleotides necessary for inhibiting the expression of Nogo B. Therefore, the Examiner's rejection of the claims over Bandman in view of Milner et al. and James depends entirely on the application of hindsight. Reconsideration and withdrawal of this rejection are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

In view of the above claim amendments and remarks, Applicants submit that the claims are now in condition for allowance and request that the Examiner issue a Notice to that effect.

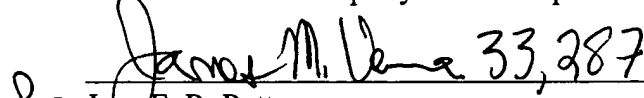


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PATENT TRADEMARK OFFICE

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 3 and 4 have been canceled.

Claims 1, 2, 5, and 23 have been amended as follows:

1. (Amended) An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding the amino acids from about 1 to about 373 of SEQ ID NO:2;

(b) a polynucleotide encoding the amino acids from about 2 to about 373 of SEQ ID NO:2;

(c) a polynucleotide encoding the amino acids from about 1 to about 197 and about 236 to about 373 of SEQ ID NO:2, wherein said amino acids about 197 and about 236 are joined by a peptide bond;

(d) a polynucleotide encoding the amino acids from about 1 to about 288 and about 336 to about 373 of SEQ ID NO:2, wherein said amino acids about 288 and about 336 are joined by a peptide bond;

(e) a polynucleotide encoding the amino acids from about 1 to about 197, amino acids about 236 to about 288, and amino acids about 336 to about 373 of SEQ ID NO:2, wherein said amino acids about 197 and about 236 are joined by a peptide bond, and said amino acids about 288 and about 336 are joined by a peptide bond;

~~(f) a polynucleotide encoding amino acids from about 198 to about 235 of SEQ ID NO:2;~~

~~(gf)~~ a polynucleotide encoding the amino acids from about 1 to about 187 of SEQ ID NO:2;

~~(hg)~~ a polynucleotide encoding the amino acids from about 2 to about 187 of SEQ ID NO:2;



(~~ih~~) a polynucleotide encoding the amino acids from about 1 to about 198 of SEQ ID NO:2;

(~~ji~~) the polynucleotide deposited as ATCC Accession No. PTA 89;

(~~ki~~) a polynucleotide at least 80% identical to any one of the polynucleotides of (a)-(~~ji~~);

(~~lk~~) the polynucleotide complement of the polynucleotide of any one of the polynucleotides of (a)-(~~ji~~).

2. (Amended) An isolated nucleic acid molecule comprising at least 10 700 contiguous nucleotides from the coding region of SEQ ID NO:1.

5. (Amended) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide wherein, except for at least one conservative amino acid substitution, said polypeptide has an amino acid sequence selected from the group consisting of:

(a) amino acids from about 1 to about 373 of SEQ ID NO:2;

(b) amino acids from about 2 to about 373 of SEQ ID NO:2;

(c) amino acids from about 1 to about 197 and about 236 to about 373 of SEQ ID NO:2, wherein said amino acids about 197 and about 236 are joined by a peptide bond;

(d) amino acids from about 1 to about 288 and about 336 to about 373 of SEQ ID NO:2, wherein said amino acids about 288 and about 336 are joined by a peptide bond;

(e) amino acids from about 1 to about 197, amino acids about 236 to about 288, and amino acids about 336 to about 373 of SEQ ID NO:2, wherein said amino acids about 197 and about 236 are joined by a peptide bond, and said amino acids about 288 and about 336 are joined by a peptide bond.

(~~f~~) ~~amino acids from about 198 to about 235 of SEQ ID NO:2;~~

(~~gf~~) amino acids from about 1 to about 187 of SEQ ID NO:2;

(~~hg~~) amino acids from about 2 to about 187 of SEQ ID NO:2; and

(~~ih~~) amino acids from about 1 to about 198 of SEQ ID NO:2.

23. (Amended) A method of inhibiting cell growth, said method comprising transfecting said cell with a polynucleotide, wherein said polynucleotide is between 8 and 50 nucleotides in length and said between 8 and 50 nucleotides are complementary to ~~the complement of a mRNA molecule encoding SEQ ID NO:2, and said polynucleotide is between about 8 and 50 nucleotides in length.~~

(JEP:cew) #29199